Amendments to the Specification

Please replace paragraph [0021] with the following amended paragraph:

[0021] With respect to steroids, such as glucocorticoids, a large dose of hydrocortisone has been shown to exacerbate an inflammatory response or to have no effect, but a smaller dose appears to have a beneficial effect even though it is not [[an]] a sufficiently effective remedy for sepsis.

Please replace paragraphs [0047] and [0048] with the following amended paragraphs:

[0047] 2) Vascular endothelial cells increase the expression of ~~Ee-seleetin~~ e-selectin by TNF-α, and interleukin-1β, and ~~Pp-seleetin~~ p-selectin by histamine and thrombin in the capillaries.

[0048] 3) Circulating white blood cells express mucins such as PSGL-1 or the tetrasaccharides sialyl Lewis and sialyl Lewis^a and sialyl Lewis^x, which bind to ~~Ee- and Pp-seleetin~~ e- and p-selectin. This binding mediates the attachment or tethering of white blood cells to the vascular endothelium, allowing the cells to roll in the direction of the blood flow (Rolling). Although p-selection and sialyl Lewis-dependent alterations are induced by leukotriene C_4/D_4 in the mid-jejunum of rats, the leukotriene receptor antagonist was not effective (Samina Kanwar et al., (1995). Since then, potent selectin inhibitors were developed;

however, they have ~~failed to do so~~ not yet succeeded (Alper J., 2001).

Please replace paragraph [0057] with the following amended paragraph:

[0057] The present inventor also discovered that dextran-induced rat paw edema was inhibited by pranlukast in a dose-dependent fashion. At a dosage of 450 mg/kg, administered intraperitoneally, pranlukast completely inhibited dextran-induced paw edema. This suggests that leukotriene C_4 and D_4 receptor antagonist acts at the endothelial cells in the capillaries and inhibits the increased permeability of the capillaries which is induced by dextran. In spite of the many openings such as clefts, fenestrae and pinocytotic vesicles in endothelial cells in the general capillary, pranlukast was found to inhibit peripherally the permeability. Since the endothelial cells in the brain capillaries have fewer openings because of the presence of the tight junctions, pranlukast may be more effective in inhibiting the permeability of brain capillaries than that of general capillaries. Therefore, it was expected that such a mechanism might also come into play at the central nervous system level.

Please replace paragraphs [0060] and [0061] with the following amended paragraphs:

[0060] The leukotriene C4 and D4 receptor antagonist pranlukast has been found to be safe (LD_{50} > 2000 mg/kg (p.o.) and (s.c.) in both rats and mice). After single administration of pranlukast (30 mg/kg, 100 mg/kg, 300 mg/kg, 1000 mg/kg; p.o.), and repeated administration of pranlukast (30 mg/kg/day, 100 mg/kg/day, 300 mg/kg/day, 1000 mg/kg/day; p.o.) for three months and six months, rats showed normal behavior, changes in body weight, and food intake compared with those of the control group. The results of urine examination and histopathological examinations are also normal by the single administration and the repeated administration of pranlukast. The maximum blood concentration of pranlukast (administered at 20 mg/kg) was attained within one hour after the administration (p.o.) and maintained for at least 5 hours. However, no pranlukast was observed 24 hours after administration of such low doses of pranlukast (data from Ono Pharmaceutical Co., Japan).

[0060] Zhang et al. (2002) reported that brain damage was induced by reperfusion 30 minutes after the occlusion of the middle cerebral artery (MCA) and was evaluated 24 hours after the reperfusion. Pranlukast (~~0.03 mg/kg~~ 0.003 mg/kg - 1.0 mg/kg) administered intraperitonealy 30 minutes before MCA and 2 hours after reperfusion inhibited the death of brain cells. However,

Zhang et al. did not study blood concentrations. Indeed, no blood concentration of pranlukast would be found at 24 hours after the reperfusion at the dose levels (0.03 mg/kg - 1.0 mg/kg) used by Zhang et al.

Please replace paragraph [0077] with the following amended paragraph:

[0077] The most common dosage form at present is an oral formulation for most presently available leukotriene antagonists because of the need to dissolve in stomach acid. Dosage forms may include tablets, troches, capsules, gel caps, lozenges, and the like. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, where solid pharmaceutical carriers are employed. In cases where the patient is unconscious, administration may preferably be by cannula to the stomach. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. At least one presently available leukotriene C4 and D4 receptor antagonist, i.e., Singulair (montelukast), can be administered intravenously. Administration can be carried out ~~two or three times a day depending on the blood concentration, but preferably only~~ once a day. Administration may be terminated when the white blood cell count in cerebrospinal fluid reaches a normal value.

Please replace paragraph [0083] with the following amended paragraph:

[0083] Pranlukast inhibits dextran-induced paw edema in rats in a dose dependent manner. The administration of arachidonic acid to the subarachnoid space causes ~~sepsis and~~ inflammation. However, pranlukast (p.o.) administered before arachidonic acid administration to the subarachnoid space inhibits ~~sepsis and~~ inflammation. This may explain why pranlukast is effective and is different from anti-inflammatory therapies and anti-endotoxin therapies.

Please replace paragraph [0087] with the following amended paragraph:

[0087] To investigate the role of leukotriene antagonists in the treatment of ~~sepsis~~ inflammation, a sensitive and quantitative method to measure inflammation for the central nervous system was developed. Important changes in the inflammatory process can be monitored, as both the permeability of BBB and the infiltration of white blood cells (WBC) to cerebrospinal fluid (CSF) caused by arachidonic acid can be measured over time from the same experimental animal. In particular, the effect of the leukotriene C_4 and D_4 antagonist, pranlukast, was studied using this method. Changes in the inflammatory process of both the permeability of BBB and the

infiltration of white blood cells (WBC) caused by administering arachidonic acid as a nociceptive stimulus were observed.

Please replace the heading before paragraph [0095] with the following amended heading:

Evaluation of the increases of the permeability of endothelial cells in the brain capillaries and WBC infiltration to the CSF during ~~sepsis~~ inflammation

Amendments to the Drawings:

The attached sheet of drawings includes changes to Fig. 2. This sheet, which includes Fig. 2, replaces the original sheet including Fig. 2.

Attachment: Replacement Sheet